RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2021, **11**, 13030

Dual C–H activation: Rh(III)-catalyzed cascade π-extended annulation of 2-arylindole with benzoquinone†

Qijing Zhang,‡ Qianrong Li‡ and Chengming Wang *

Received 6th March 2021
Accepted 26th March 2021

DOI: 10.1039/d1ra01779a

rsc.li/rsc-advances

A rhodium-catalyzed, N–H free indole directed cyclization reaction of benzoquinone *via* a dual C–H activation strategy is disclosed. This protocol has a good functional group tolerance and affords useful indole-fused heterocylces. Besides, it is insensitive to moisture, commercially available solvent can be directly used and work quite well for this transformation.

Quinones are widely distributed in nature, and commonly occur in bacteria, flowering plants and arthropods (Fig. 1). They have a wide range of applications, including diverse important pharmacological properties, involvement in redox reactions and development for advanced electrochemical energy storage.[1] Among varied reported quinones, benzoquinone (BQ) is the simplest and most important one. It has been well reported that BQ has a significant and unique role in oxidative palladium(II)-catalyzed coupling reactions.[2] The chemistry of benzoquinone has been extensively explored in detail, including nucleophilic addition and cycloaddition reactions, photochemistry and oxidative coupling.[1b,c,2] Although great achievements have been obtained, only a few examples are disclosed about BQ as a reactant applying to transition-metal catalyzed C–H functionalization.[1e] Among the examples reported, cyclization or BQ direct functionalization products were mainly afforded (Scheme 1a).

Transition-metal catalyzed C–H functionalization has undergone great progresses in the past two decades.[3] In order to get a better reactivity and controlled selectivity, a directing group is usually needed for this process. Therefore, various directing groups have been developed.[4] However, many of them (*e.g.* various nitrogen-containing heterocycles) remained parts of products after reaction, therefore increasing the procedures and difficulty for structure further modification and manipulation.[5] As a result, it is highly demanded to explore traceless or easily removable directing groups.[6] In this context, N–H free indole moiety has gradually emerged as a versatile functionalizable directing group in transition-metal catalyzed cyclization reaction.[7]

On the other hand, although the above-mentioned great breakthrough obtained in C–H functionalization, there are few examples reported for dual C–H activation reactions.[8] During our research program exploring transition-metal catalysis and heterocyclic synthesis,[9] we intended to prepare the indole-

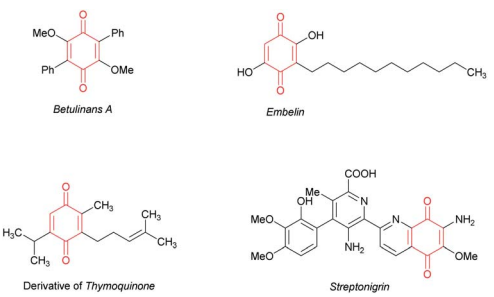
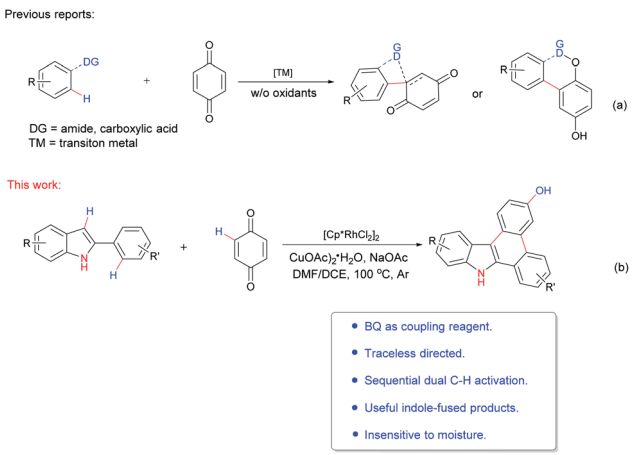


Fig. 1 Selected examples of bioactive molecules containing the benzoquinone moiety.



Scheme 1 Transition-metal catalyzed C–H functionalization of BQ.

Department of Chemistry, College of Chemistry and Materials Science, Jinan University, Guangzhou, 511443, China. E-mail: cmwang2019@jnu.edu.cn

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra01779a

‡ Contributed equally to this work.

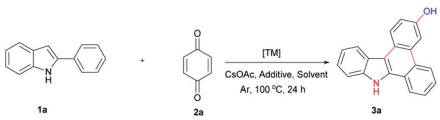
containing heterocycles based on the consideration of their potential biological activity. Herein, we report a rhodium-catalyzed N–H free indole directed annulation reaction with BQ through dual C–H activation strategy (Scheme 1b).

Our initial study was carried out by examining 2-phenyl indole **1a** and benzoquinone **2a** in the presence of [{Cp*RhCl$_2$}$_2$] and Cu(OAc)$_2$·H$_2$O in commercial available *N*,*N*-dimethylformamide under argon atmosphere. To our delight, the desired 9*H*-dibenzo[*a*,*c*]carbazol-3-ol product **3a** was isolated in 55% yield (Table 1, entry 1). Further investigation showed the reaction did not occur in the absence of copper additive (Table 1, entry 2). DMF appears to be the best solvent for this transformation, other solvents such as DMAc, DMSO and *t*-Amyl-OH did not participate in this transformation (Table 1, entry 4–6) [{Cp*RhCl$_2$}$_2$] proved to be crucial to this reaction, other catalysts only gave trace product (Table 1, entry 3, 7–9). Several other additives were tested, all of them shut down this transformation (Table 1, 10–12). The optimized conditions were eventually identified as (Table 1, entry 13): 1.5 equiv. 2-phenyl indole, 1.0 equiv. BQ, 5 mol% [{Cp*RhCl$_2$}$_2$], 2 equiv. NaOAc, and 2.1 equiv. Cu(OAc)$_2$·H$_2$O.

With the optimized conditions in hand, we next tend to examine the substrates scope of this reaction. Various 2-aryl indoles with electron-rich substituted groups were tested and worked well for this reaction (Table 2, **3b–g**); in some cases, the reaction temperature could even be lowered to 60 °C. Halogens did not interfere with this transition-metal catalyzed process, affording the desired products smoothly (Table 2, **3h–k**, **3p–r**). Substrates with strong electron-withdrawing groups (**3l**, **3n**), such as nitro-, trifluoromethyl, also proceeded regularly in this transformation. Interestingly, substrate containing other directing group such as amide group could also produce the related product **3n** in 64% yield, with quite excellent regioselectivity.[10] Finally, an interesting S, N-fused heterocycle **3m** was obtained when 2-thienyl indole was employed. Other derivatives of benzoquinone such as 1,4-naphthaquinone or methyl-*p*-benzoquinone currently failed to produce the related cyclization products with proper yields.

In addition, this method allows quick access to a number of functional heterocycles (Scheme 2).[7g,11] For example, the hydroxyl group can be easily removed to afford 9*H*-dibenzo[*a*,*c*]carbazole **4a** which can be further converted into organic electroluminescent element **5a** *via* reported methods.[11]

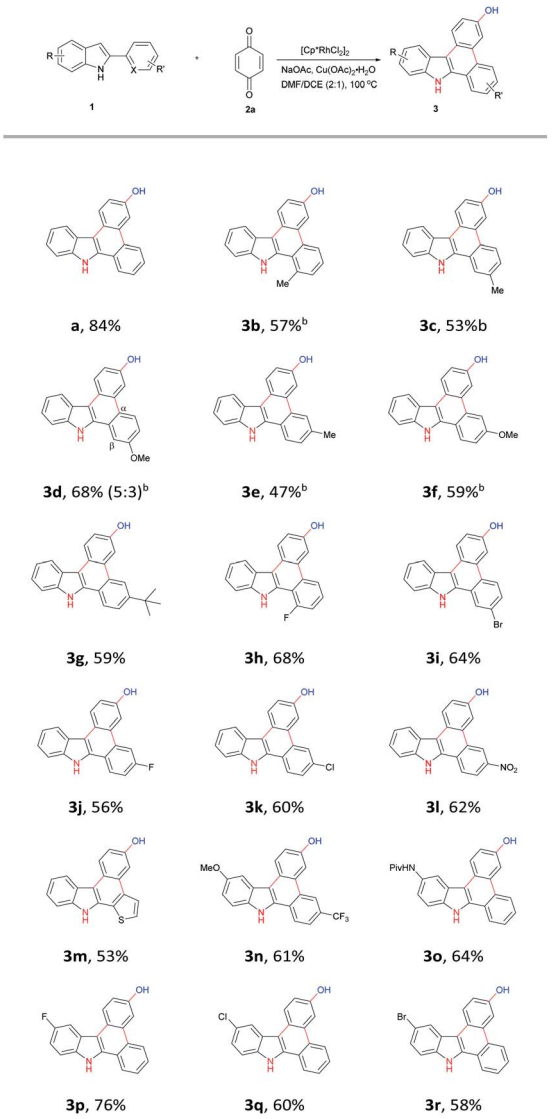
Table 1 Conditions optimization[a]a



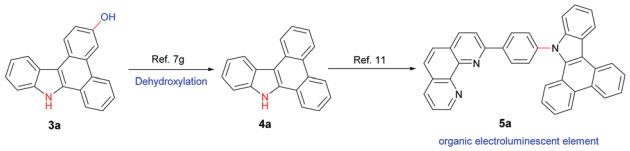
Entry	Solvent	Catalyst	Additive	Yield
1	DMF	[Cp*RhCl$_2$]$_2$	Cu(OAc)$_2$·H$_2$O	55%
2	DMF	[Cp*RhCl$_2$]$_2$	—	<5%
3	DMF	—	Cu(OAc)$_2$·H$_2$O	—
4	*t*-Amyl-OH	[Cp*RhCl$_2$]$_2$	Cu(OAc)$_2$·H$_2$O	—
5	DMAc	[Cp*RhCl$_2$]$_2$	Cu(OAc)$_2$·H$_2$O	<5%
6	DMSO	[Cp*RhCl$_2$]$_2$	Cu(OAc)$_2$·H$_2$O	Trace
7	DMF	[RuCl$_2$(*p*-cymene)]$_2$	Cu(OAc)$_2$·H$_2$O	—
8	DMF	Pd(OAc)$_2$	Cu(OAc)$_2$·H$_2$O	—
9	DMF	RhCl(PPh$_3$)$_3$	Cu(OAc)$_2$·H$_2$O	<5%
10	DMF	[Cp*RhCl$_2$]$_2$	AgOAc	—
11	DMF	[Cp*RhCl$_2$]$_2$	Ag$_2$O	—
12	DMF	[Cp*RhCl$_2$]$_2$	Cu(acac)$_2$	Trace
13[b]b,[c]c	DMF/DCE	[Cp*RhCl$_2$]$_2$	Cu(OAc)$_2$·H$_2$O	**84%**

[a] Reaction on a 0.2 mmol scale, using **1a** (1.0 equiv.), **2a** (1.0 equiv.), additive (2.0 equiv.), CsOAc (2.0 equiv.), [TM] (5 mol%), solvent (1.0 mL), under N$_2$, isolated yield. [b] **1a** (1.5 equiv.), solvent (0.3 M). [c] NaOAc was used instead of CsOAc.

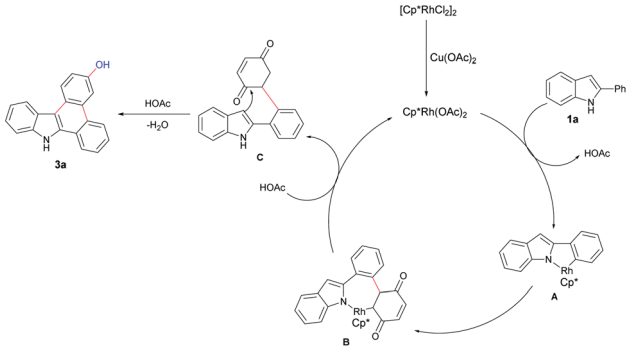
Table 2 Substrates scope[a]



[a] Condition A: 2-aryl indole (1.5 equiv.), BQ (1.0 equiv.), [Rh] (5 mol%), Cu(OAc)$_2$·H$_2$O (2.1 equiv.), NaOAc (2.0 equiv.), DMF/DCE(1.5 mL, 2 : 1), 100 °C. [b] Condiiton B: 2-aryl indole (1.0 equiv.), BQ (2.0 equiv.), [Rh] (5 mol%), Cu(OAc)$_2$·H$_2$O (2.1 equiv.), NaOAc (2.0 equiv.), DMF/DCE(1.5 mL, 2 : 1), 60 °C.



Scheme 2 Diversity of the product.



Scheme 3 Proposed mechanism.

Finally, we proposed a mechanism for this transformation (Scheme 3) based on reported literatures.[7,9a–c,12] First, [{Cp*RhCl$_2$}$_2$] dissociates and delivers the active catalyst monomer [Cp*Rh(OAc)$_2$] with the assistance of copper acetate and sodium acetate.[9a–c] C–H activation of 2-phenyl indole by Rh(III) produces rhodacyclic intermediate **A**,[7] followed by insertion of benzoquinone affording intermediate **B**, which can be transformed into **C** *via* two folds protonation and fulfills the catalytic cycle. The final product **3a** can be easily accessed *via* intramolecular condensation of **C**.[7g]

In conclusion, we have developed a Rh(III)-catalyzed traceless directed dual C–H activation of 2-aryl indole and annulation with benzoquinone affording indole-fused heterocycles. The protocol is applicable to a wide range of indole derivatives, affording related products in middle to good yields. Further exploration of the synthetic utilities of this chemistry and detailed mechanistic study are currently in progress in our lab and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by "the Fundamental Research Funds for the Central Universities" (21620318, 2019QNGG22). We thank the Jinan University (start-up fund) for additional support.

Notes and references

1 For related reviews, see: (*a*) P. R. Dandawate, A. C. Vyas, S. B. Padhye, M. W. Singh and J. B. Baruah, *Mini-Rev. Med. Chem.*, 2010, **10**, 436; (*b*) I. Abraham, R. Joshi, P. Pardasani and R. T. Pardasani, *J. Braz. Chem. Soc.*, 2011, **22**, 385; (*c*) V. Nair, R. S. Menon, A. T. Biju and K. G. Abhilash, *Chem. Soc. Rev.*, 2012, **41**, 1050; (*d*) C. Han, H. Li, R. Shi, T. Zhang, J. Tong, J. Lia and B. Li, *J. Mater. Chem. A*, 2019, **7**, 23378; (*e*) J. M. Wood, R. L. de Carvalho and E. N. d. S. Júnior, *Chem. Rec.*, 2021, **21**, 1.

2 (*a*) A. Vasseur, J. Muzart and J. L. Bras, *Eur. J. Org. Chem.*, 2015, 4053; (*b*) B. Yang, Y. Qiu and J.-E. Bäckvall, *Acc. Chem. Res.*, 2018, **51**, 1520.

3 For selected reviews, see: (*a*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (*b*) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev.*, 2016, **45**, 2900; (*c*) O. Eisenstein, J. Milani and R. N. Perutz, *Chem. Rev.*, 2017, **117**, 8710; (*d*) Z. Dong, Z. Ren, S. J. Thompson, Y. Xu and G. Dong, *Chem. Rev.*, 2017, **117**, 9333; (*e*) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev.*, 2019, **119**, 2192.

4 Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.*, 2015, **2**, 1107.

5 R. L. Carvalho, R. G. Almeida, K. Murali, L. A. Machado, L. F. Pedrosa, P. Dolui, D. Maiti and E. N. d. S. Júnior, *Org. Biomol. Chem.*, 2021, **19**, 525.

6 (*a*) G. Rousseau and B. Breit, *Angew. Chem., Int. Ed.*, 2011, **50**, 2450; (*b*) C. Wang and Y. Huang, *Synlett*, 2013, **24**, 145; (*c*) G. Rani, V. Luxami and K. Paul, *Chem. Commun.*, 2020, **56**, 12479.

7 (*a*) K. Morimoto, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2010, **12**, 2068; (*b*) L. Ackermann, L. Wang and A. V. Lygin, *Chem. Sci.*, 2012, **3**, 177; (*c*) B. Li, B. Zhang, X. Zhang and X. Fan, *Chem. Commun.*, 2017, **53**, 1297; (*d*) Y.-Q. Xia and L. Dong, *Org. Lett.*, 2017, **19**, 2258; (*e*) X. Yang, Y. Li, L. Kong and X. Li, *Org. Lett.*, 2018, **20**, 1957; (*f*) S. Guo, Y. Liu, Y. Wang, X. Zhang and X. Fan, *J. Org. Chem.*, 2020, **85**, 8910. During the preparation of this manuscript, an example of Rh(III)-catalyzed oxidative annulation of 2-arylindole with BQ under high temperature (at 140 °C) using chlorobenzene as solvent was reported, see: (*g*) S. Guo, Y. Liu, L. Zhao, X. Zhang and X. Fan, *Org. Lett.*, 2019, **21**, 6437.

8 For selected recent examples, see: (*a*) L. Zhang, Y. Wang, Y. Shi, Y. Wu, J. Lan, W. Ma and J. You, *ACS Catal.*, 2019, **9**, 5358; (*b*) M. Uryu, T. Hiraga, Y. Koga, Y. Saito, K. Murakami and K. Itami, *Angew. Chem., Int. Ed.*, 2020, **59**, 6551; (*c*) K. Ghosh, Y. Nishii and M. Miura, *Org. Lett.*, 2020, **22**, 3547; (*d*) A. D. Streit, A. J. Zoll, G. L. Hoang and J. A. Ellman, *Org. Lett.*, 2020, **22**, 1217.

9 (*a*) C. Wang, H. Chen, Z. Wang, J. Chen and Y. Huang, *Angew. Chem., Int. Ed.*, 2012, **51**, 7242; (*b*) C. Wang and Y. Huang, *Org. Lett.*, 2013, **15**, 5294; (*c*) C. Wang, H. Sun, Y. Fang and Y. Huang, *Angew. Chem., Int. Ed.*, 2013, **52**, 5795; (*d*) C. Wang, A. Wang and M. Rueping, *Angew. Chem., Int. Ed.*, 2017, **56**, 9935; (*e*) C. Wang and M. Rueping, *ChemCatChem*, 2018, **10**, 2681; (*f*) C. Wang, B. Maity, L. Cavallo and M. Rueping, *Org. Lett.*, 2018, **20**, 3105; (*g*) W. Zhang, C. Wang and Q. Wang, *ACS Catal.*, 2020, **10**,

13179; (*h*) C. Wang and L. Liu, *Org. Chem. Front.*, 2021, DOI: 10.1039/d0qo01508c.

10 Amide has been reported to act as a directing group, see: R.-Y. Zhu, M. E. Farmer, Y.-Q. Chen and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2016, **55**, 10578.

11 J. R. Lee, K. Park, J. S. Yu, S. G. Lee, E. Cho and J. Lee, *PCT Int. Appl.*, 2018, WO2018092927A1.

12 T. Satoh and M. Miura, *Chem.–Eur. J.*, 2010, **16**, 11212.